

REMARKS AND ARGUMENTS

Claims 1, 5, and 6 are under prosecution in this case. Claims 1 and 5 have been amended to better claim the subject matter which Applicant regards as the invention. Claim 6 is a rewritten version of claim 4 for improved clarity. Claims 2-4 have been canceled without prejudice. No new matter has been added with this Amendment.

Claim Rejections under 35 U.S.C. § 112:

Claims 1-5 are rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the Specification, while being enabling for a method for preparing a factor VIII molecule having a specific mutation disclosed in the Specification, does not provide enablement for a method for preparing a factor VIII protein having modified glycosylation comprising making a mutation anywhere in the protein sequence and thus does not enable a person skilled in the art to make and use the invention. Applicant respectfully traverses this rejection.

Without acquiescing to this aspect of the rejection, claim 1 has been amended and claims 2-4 have been canceled without prejudice. Claim 4 has been rewritten as new claim 6 for improved clarity. Amended claim 1 specifically defines that a mutation encoding a glycosylation site be introduced either to the A2 or C2 domain of the factor VIII protein and the modified factor is biologically active.

Applicant maintains that one of ordinary skill in the art can make and use the invention based on the disclosure provided herein combined with the knowledge available in the art.

The invention was based on the inventor's studies that a less immunogenic factor VIII protein was produced when the factor VIII was modified to be glycosylated at a certain location in the A2 domain, as demonstrated in the Specification. The development of inhibitory antibodies to factor VIII has been a serious problem in the management of patients with hemophilia A. A majority of inhibitory antibodies present in such patients have been shown to

be directed to the A2 or C2 domains. Therefore, the invention provides a new means of producing a less antigenic factor VIII that is useful in the management of patients with hemophilia A.

Applicant disagrees with the allegation in the Office Action that the experimentation required to practice the invention is undue. The level of the skill and the knowledge in the relevant art (i.e., molecular biology and biochemistry) is high and all the necessary protocols are readily available to one of ordinary skill in the art to make and use the invention. Claim 1 as amended herein defines the modification to be either to the A2 or C2 domain. The location and the amino acid as well as the nucleotide sequences of these domains are well known in the art. One skilled in the art would have known how to introduce a mutation encoding a glycosylation recognition sequence to a desired location in either of these two domains, express a mutant factor VIII, and assay for biological activity. It is clearly defined in all the claims that a modified factor VIII produced according to the invention be biologically active. The biological activity of a newly produced factor VIII can be easily measured by employing one of many available assays in the art. One skilled in the art would not need further guidance or direction to practice the invention.

The Office Action maintains the rejection by citing Aly *et al.* Aly *et al.* reported two mutants, biologically inactive factor VIII proteins, one of which contains an added glycosylation site in the A2 domain. However, it is also stated therein that "[T]he loss of protein function as a result of abnormal additional glycosylation is a rare cause of clinical disorder" (*see* page 4936, last paragraph in the left column). Further, the authors emphasize the fact that the role of carbohydrate in factor VIII function appears to be dispensable.

The claimed invention is a method of producing a biologically active factor VIII protein having modified glycosylation. In view of the amendments made herein, it is submitted that one of ordinary skill in the art would have been able to make and use the invention based on the

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disclosure combined with the knowledge available in the art, without undue experimentation.
Withdrawal of the rejection under 35 U.S.C. §112 is respectfully requested.

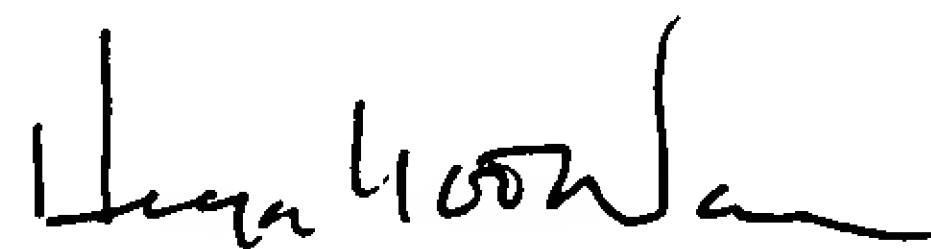
Conclusion:

Based on the foregoing amendments and arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (three months) and a check in the amount of \$930.00 in payment of the fees therefor. If the amount is incorrect, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,



Heeja Yoo-Warren
Reg. No. 45,495

GREENLEE, WINNER AND SULLIVAN, P.C.
5370 Manhattan Circle, Suite 201
Boulder, CO 80303
Telephone: (303) 499-8080
Facsimile: (303) 499-8089
E-mail: winner@greenwin.com
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